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(54) **Title of the Invention:** Pyrimidine derivative or salt thereof

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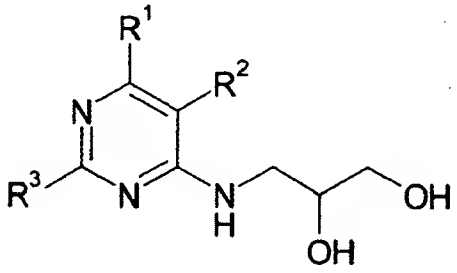
[Selected Figure] None

(57) **[Abstract]**

[Problem to Be Solved] To provide a compound having an excellent effect of promoting insulin secretion and an effect of suppressing blood sugar rise, which can be used in the treatment of insulin-dependent diabetes, non-insulin-dependent diabetes, insulin resistance diseases and obesity.

[Means for Solving the Problems] The pyrimidine derivative shown in Formula (I) or a pharmaceutically acceptable salt thereof.

[Formula 1]



(I)

[In the formula, the reference symbols have the following meanings.]

R^1: methyl, ethyl or cyclopropyl, each of which may be substituted by one or more halogen, which may be the same or different.

R^2: -H, -F or methyl.

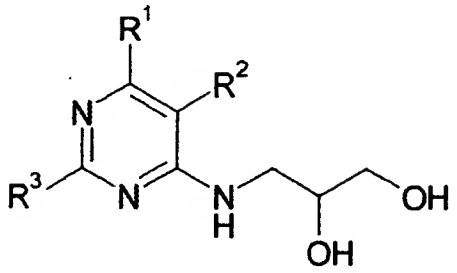
R^3: an aryl, or aromatic heterocycle, each of which may be substituted.]

[CLAIMS]

[Claim 1]

The pyrimidine derivative shown in Formula (I) or a pharmaceutically acceptable salt thereof.

[Formula 1]



(I)

[In the formula, the reference symbols have the following meanings.]

R^1: methyl, ethyl or cyclopropyl, which may be substituted by one or more halogen, which may be the same or different.

R^2: -H, -F or methyl.

R^3: an aryl, or aromatic heterocycle, each of which may be substituted.

[Claim 2]

The pyrimidine derivative shown in Formula (I) according to Claim 1, or a pharmaceutically acceptable salt thereof, with the exception of the following compounds:

3-{[2-(4-bromophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(3-chloro-4-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(2,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(3,4-difluorophenyl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(3,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(3,4,5-trifluorophenyl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(4-chloro-2-fluorophenyl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(4-chloro-3-fluorophenyl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(4-bromophenyl)-5-fluoro-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(5-bromo-2-fluorophenyl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(2,1,3-benzoxadiazol-5-yl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(2,3,5-trifluorophenyl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(2,5-difluorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(3,4-difluorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(3,4,5-trifluorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(4-chlorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(3,4-dichlorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(4-chloro-2-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(4-chloro-3-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(5-bromo-2-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(2,1,3-benzoxadiazol-5-yl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol; and

3-{[2-(2,3,5-trifluorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol.

[Claim 3]

A pharmaceutical composition having as an active ingredient a compound shown in Formula (I) according to Claim 1.

[Detailed Description of the Invention]

[0001]

[Technical Field of the Invention]

The present invention relates to a pharmaceutical agent and particularly to a novel pyrimidine derivative, or a pharmaceutically acceptable salt thereof, useful as an agent for promoting insulin secretion or an agent for treating diabetes, and to a medicament having these compounds as an active ingredient thereof.

[0002]

[Prior Art]

Diabetes is a disease primarily characterized by chronic hyperglycemia that develops as a result of relatively or absolutely insufficient insulin action. Clinically, it is broadly divided according to characteristics into insulin-dependent diabetes (hereinafter referred to as "type 1 diabetes") and non-insulin-dependent diabetes (hereinafter referred to as "type 2 diabetes"). One of the major critical causes of type 2 diabetes, which accounts for approximately 90% of diabetics, is decreased insulin secretion from pancreatic β-cells; in particular, postprandial hyperglycemia is observed to result from initial insulin secretion deficiency. Presently, sulphonylurea agents (SU agents) are commonly used as insulin secretion promoters, but these tend to produce hypoglycemia and are known to cause secondary failure due to pancreatic exhaustion in long-term administration. Furthermore, while SU agents are effective for control of blood sugar between meals, suppressing postprandial hyperglycemia is difficult. Recently, large-scale clinical trials have confirmed that correction of postprandial hyperglycemia is important in the development of diabetic complications and in controlling progression (Non-Patent Document 1). Furthermore, it has been reported that arterial sclerosis occurs only in the postprandial hyperglycemia period and that persistent mild postprandial hyperglycemia increases death rates due to cardiovascular causes and the like (Non-Patent Document 2). This indicates that, even if mild, postprandial hyperglycemia is an independent risk factor in cardiovascular death. The background described above has resulted in the acknowledgment of the importance and necessity of drug therapies for postprandial hyperglycemia. Accordingly, a pharmaceutical agent having an insulin secretion promoting effect has a profile suitable for correcting postprandial hyperglycemia and/or fasting blood sugar, and may be useful as a therapeutic and prophylactic agent for type 1 diabetes and type 2 diabetes.

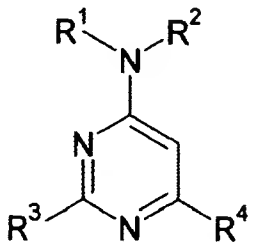
[0003]

Meanwhile, 2,6-dimethyl-4-(2,3-dihydroxypropyl)aminopyrimidine is known as a pyrimidine derivative serving as an intermediate in the production of compounds having an antimicrobial effect (Patent Document 1).

Furthermore, the compound shown in the following general formula is known as an agent used in the

treatment of disorders of the circulatory system such as hypertension (Patent Document 2).

[Formula 2]



(See the publication for reference numerals in the formula.) Note that, in Patent Document 2, diabetes is mentioned as one example of various diseases other than circulatory diseases such as hypertension, but this is not supported by data.

Moreover, in this bulletin, R^4 in the general formula is described in the claims as being a "(C_2-C_5)-alkyl, a trifluoromethyl or an aryl," but specific disclosure in the embodiments is limited to isopropyl, trifluoromethyl, tertiary butyl and phenyl compounds. Furthermore, in this bulletin, 2-hydroxyethyl, 3-hydroxypropyl and 4-hydroxybutyl are specifically disclosed for R^1 and R^2 in the general formula, but no specific disclosure is made of compounds having two hydroxyl groups or compounds having secondary hydroxyl groups.

[0004]

[Non-Patent Reference 1] *N. Engl. J. Med.,* 329: 977-986, 1993

[Non-Patent Reference 2] *Lancet,* 354:617, 1999, *Brit. Med. J.,* 321: 405-413, 2000

[Patent Reference 1] International Publication WO 95/11899

[Patent Reference 2] Specification of Unexamined European Patent Application EP 1112266

[0005]

[Problems to Be Solved by the Invention]

As described above, agents for promoting insulin secretion are useful in the treatment and prevention of type 1 diabetes, type 2 diabetes, insulin resistance diseases and obesity; there is therefore a demand for the creation of an agent for promoting insulin secretion having even greater effectiveness.

[0006]

[Means for Solving the Problems]

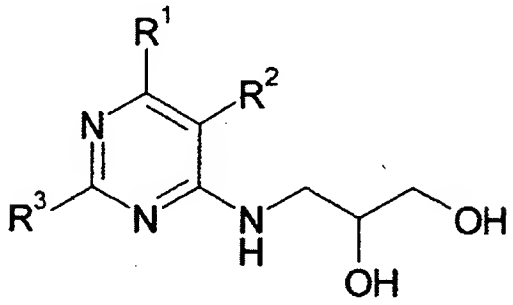
The present inventors earnestly studied compounds having insulin secretion promotion effects and discovered that a pyrimidine derivative had excellent insulin secretion promotion effects, and thus the present invention was completed.

[0007]

In other words, according to the present invention, the pyrimidine derivative shown in Formula (I), a

pharmaceutically acceptable salt thereof, and a pharmaceutical composition having these compounds as an active ingredient, are provided.

[Formula 3]



(I)

[In the formula, the reference symbols have the following meanings.]

R^1: methyl, ethyl or cyclopropyl, which may be substituted by one or more halogen, which may be the same or different.

R^2: -H, -F or methyl.

R^3: an aryl, or aromatic heterocycle, each of which may be substituted.

Preferably, the pyrimidine derivative shown in Formula (I), or a pharmaceutically acceptable salt thereof, is provided, with the exception of the following compounds.

3-{[2-(4-bromophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(3-chloro-4-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(2,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(3,4-difluorophenyl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(3,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(3,4,5-trifluorophenyl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(4-chloro-2-fluorophenyl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(4-chloro-3-fluorophenyl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(4-bromophenyl)-5-fluoro-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(5-bromo-2-fluorophenyl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(2,1,3-benzoxadiazol-5-yl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(2,3,5-trifluorophenyl)-6-methylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(2,5-difluorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(3,4-difluorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(3,4,5-trifluorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(4-chlorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(3,4-dichlorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(4-chloro-2-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(4-chloro-3-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(5-bromo-2-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol;

3-{[2-(2,1,3-benzoxadiazol-5-yl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol; and

3-{[2-(2,3,5-trifluorophenyl)-6-ethylpyrimidine-4-yl]amino}propane-1,2-diol.

[0008]

Note that, in Formula (I), R^1 is preferably methyl which may be substituted by one or more halogens, which are the same or different, or ethyl substituted by one or more halogens, which are the same or different, (with the exception of trifluoromethyl), and is more preferably methyl.

Furthermore, in Formula (I) R^2 is preferably –H.

Note that, in Formula (I) R^3 is preferably a phenyl or a pyridyl substituted by one or more halogens, which are the same or different, more preferably a phenyl substituted by two to four halogens, which are the same or different, and particularly preferably a phenyl substituted by two to four halogens, which are the same or different, including at least one fluorine.

[0009]

The compound of the present invention shown in Formula (I) is characterized in terms of chemical structure by the fact that the amino group in position 4 of the pyrimidine is substituted by a 2,3-dihydroxypropyl group, and is pharmaceutically characterized by having an effect of promoting insulin secretion.

[0010]

[Modes of Embodiment of the Invention]

The compound represented by Formula (I) is as described hereinafter.

"Aryl" means a univalent C_{6-14} aromatic hydrocarbon ring group that is mono to tricyclic, preferably phenyl or naphthyl, and more preferably phenyl. "Aromatic heterocycle" means a univalent aromatic heterocyclic group, which may be condensed with benzene ring having one to four identical or different heteroatoms selected from the group consisting of nitrogen, oxygen, and sulphur, specifically, pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, furazanyl, pyridyl, pyranyl, thiopyranyl, pyridazyl, pyrimidyl, pyrazyl, indolyl, isoindolyl, indolizinyl, benzofuryl, benzothienyl, benzoimidazolyl, indazolyl, benzooxazolyl, benzothiazolyl, benzooxadiazolyl, quinolyl, isoquinolyl, chromenyl, benzothiopyranyl, phthalazinyl, naphthylizinyl, quinoxalinyl, quinoxazolinyl, cinnolinyl, benzodioxolyl, benzodioxinyl, benzodioxepinyl, carbazolyl, or the like; the nitrogen and the sulphur atoms that constitute these rings may be oxidized; in addition, these rings may be partially saturated. Pyridyl, furyl, thienyl, imidazolyl, thiazolyl, oxidopyridyl, pyrazyl, indolyl, benzofuryl, benzothienyl, benzoimidazolyl, benzooxazolyl, benzothiazolyl, benzooxadiazolyl, quinolyl, oxidoquinolyl, isoquinolyl, chromenyl, benzodioxolyl, benzodioxinyl, and benzodioxepinyl are preferred.

"Halogen" includes fluoro-, chloro-, bromo- and iodo-. Fluoro-, chloro- and bromo- are preferred.

[0011]

In the present specification, substituents acceptable [as relates to] the term, "which may be substituted," or, "substituted," can be any substituent normally used as a substituent for these groups, and may include more than one substituent for each of these groups. Substituents acceptable in terms of "aryl or aromatic heterocycles, which may each be substituted" for R^3, include the groups cited in (1) to (8) below. Note that "R^A" indicates a lower alkyl, which may be substituted by one or more groups selected from the group consisting of -OH, -O-lower alkyl, amino which may be substituted by one or two lower alkyls, carbonyl which may be substituted by one or two lower alkyls, aryl, an aromatic heterocycle and halogen.

(1) halogen;

(2) -OH, -O-R^A, -O-aryl, -OCO-R^A, oxo(=O);

(3) -SH, -S-R^A, -S-aryl, -SO-R^A, -SO-aryl, -SO_2-R^A, -SO_2-aryl, sulfamoyl, which may be substituted by one or two of R^A;

(4) an amino, which may be substituted by one or two of R^A, -NHCO-R^A, -NHCO-aryl, -$NHCO_2$-R^A, -$NHCONH_2$, -NHCONH-R^A, -$NHSO_2$-R^A, -$NHSO_2$-aryl, nitro;

(5) -CHO, -CO-R^A, -CO_2H, -CO_2-R^A, cyano or carbamoyl, which may be substituted by one or two of R^A;

(6) aryl or cycloalkyl, each of which may be substituted by one or more groups selected from the group consisting of: -OH, -O-lower alkyl, amino, which may be substituted by one or two of R^A, halogen and R^A;

(7) aromatic heterocycle or a non-aromatic heterocycle, which may be substituted by one or more groups selected from the group consisting of: -OH, -O-lower alkyl, amino, which may be substituted by one or two of R^A, halogen and R^A;

(8) lower alkyl, which may be substituted by one or more groups selected from the groups set forth in (1) to (7) above.

Herein, the term "lower alkyl" refers to a C_{1-6} alkyl, and specific examples are methyl, ethyl, propyl, butyl, pentyl, or structural isomers thereof, such as hexyl, isopropyl, isobutyl or the like; C_{1-4} alkyls are preferred, and methyl and ethyl are more preferred.

Furthermore, "cycloalkyl" refers to a univalent C_{3-10} carbocyclic group, and these rings may be crosslinked. Specific examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, norbornyl, and adamanthyl.

The term "non-aromatic heterocycle" means a univalent non-aromatic heterocyclic group having one to four heteroatoms chosen from amongst the group consisting of nitrogen, oxygen and sulfur which may be the same or different, and specific examples include: oxetanyl, pyrrolidinyl, tetrahydrofuryl, tetrahydrothiofuryl, tetrahydrothiopyranyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperadinyl,

morpholinyl, thiomorpholinyl, and quinuclidinyl; the nitrogen and the sulphur atoms that constitute these rings may be oxidized. Pyrrolidinyl, piperidinyl, piperadinyl, and morpholinyl are preferred.

[0012]

The compound represented by Formula (I), depending on the type of substituents, may contain an asymmetric carbon atom, and an optically active substance may exist as a result.

In addition, there may be cases where the compounds shown by Formula (I) form salts, which are included in the present invention, as long as such salts are salts that are pharmaceutically acceptable. Specifically, acid addition salts of inorganic acids, such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, and phosphoric acid, organic acids, such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, aspartic acid, and glutamic acid, salts of inorganic bases containing metals, such as sodium, potassium, magnesium, calcium, and aluminum, salts of organic bases, such as methylamine, ethylamine, ethanolamine, lysine, and ornithine, and ammonium salts and the like may be cited.

Furthermore, the present invention also includes substances comprising various hydrates, solvates, or crystal polymorphs of the compound that is the active ingredient of the pharmaceutical agent of the present invention or the compound of the present invention or pharmaceutically acceptable salts thereof. In addition, the compound that is the active ingredient of the pharmaceutical agent of the present invention or the compound of the present invention also includes all compounds that are metabolized *in vivo* and converted into the compounds shown by Formula (I) or the salt thereof, so-called prodrugs. As groups that form prodrugs of the compound that is the active ingredient of the pharmaceutical agent of the present invention or the compound of the present invention, the groups described in *Prog. Med.* 5:2157-2161 (1985) and groups described in "Development of Pharmaceuticals," volume 7, *Molecular Design,* pp. 163-198, Hirokawa Shoten (1990) may be cited.

[0013]

Manufacturing Method

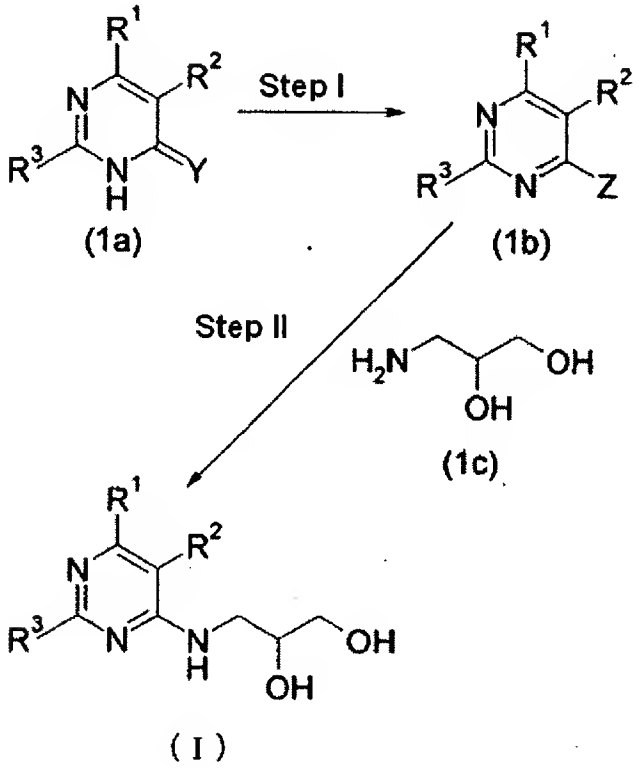
The compound shown by Formula (I) or the salt thereof may be manufactured by applying a variety of well-known synthesis methods using characteristics that are based on the basic backbone or the type of substituents. Representative preparations are illustrated below. In addition, depending on the type of functional group, there may be cases where it is effective, in terms of manufacturing technology, to replace, at the raw material or intermediate stage, the functional group in question with a suitably protected group, i.e., a group that can be easily reverted into the functional group in question. Thereafter, the protective group can be eliminated as necessary to obtain the desired compound. For example, such functional groups include the hydroxyl group or the carboxyl group or the amino group, and protective groups therefor include the protective groups described, for instance, in *Protective Groups in Organic*

Synthesis, 3rd ed., by Greene and Wuts; these may be used as is suitable according to reaction conditions.

[0014]

Preparation 1

[Formula 4]



In the formula, R^1, R^2 and R^3 have the same meaning as described above, Y indicates O or S; and Z the leaving group (same hereinafter). This preparation is a method in which a pyrimidine derivative, which has a leaving group, shown by Formula (1b), and which can be prepared by halogenation or sulfonylation of the pyrimidinone or pyrimidinethione derivative shown by Formula (1a) according to ordinary methods, is acted upon by the dihydroxypropylamine shown in Formula (1c) to manufacture the compound shown by Formula (I).

The leaving group indicated by Z in Compound (1b) represents a group which may be eliminated in the form of HZ with a hydrogen atom from the amino group of Compound (1c) under reaction conditions, and includes, for example, halogens, such as fluoro-, chloro-, bromo-, and iodo-, lower alkylsulfonyloxy groups, such as methanesulfonyloxy, perhalogenomethanesulfonyloxy groups, such as trifluoromethanesulfonyloxy, and arylsulfonyloxy groups, such as benzenesulfonyloxy and

p-toluenesulfonyloxy.

Step I Halogenation in this step is carried out by reacting, for instance, Compound (1a) with a halogenation agent, such as phosphorus oxychloride or phosphorus tribromide. Sulfonylation is carried out by reacting, for instance, Compound (1a) where Y is an oxygen atom and a sulfonylation agent, such as methanesulfonylchloride, p-toluenesulfonylchloride, trifluoromethanesulfonylchloride, or trifluoromethanesulfonic acid anhydride.

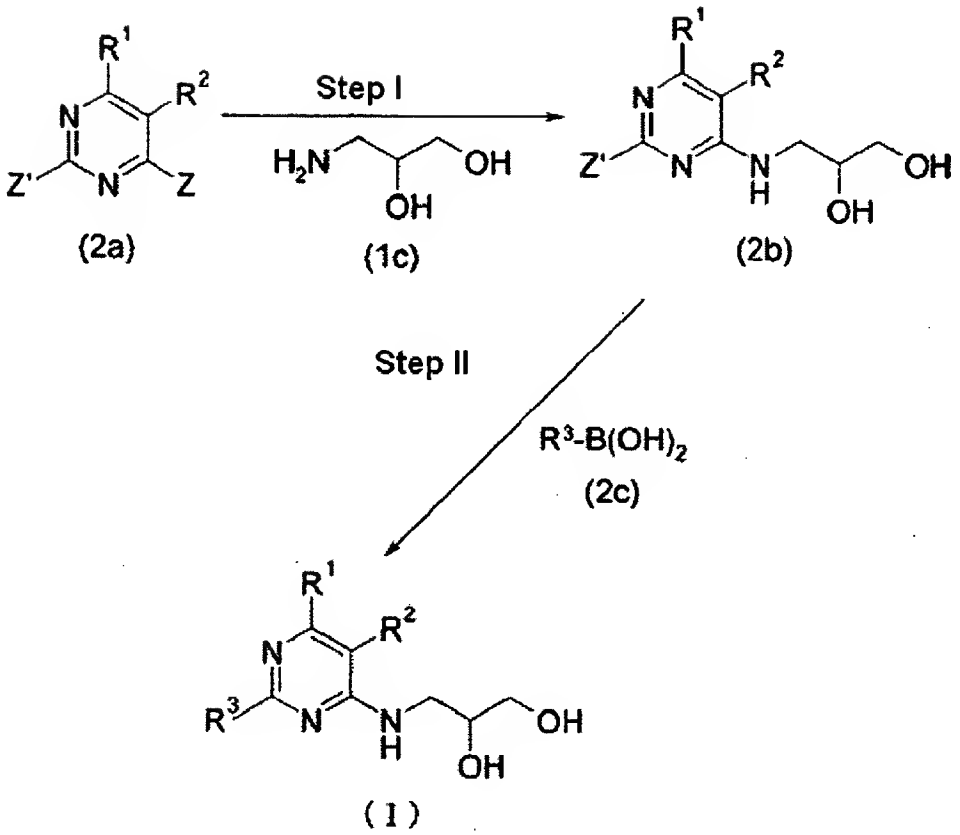
Compound (1a) can be prepared by well-known methods, for instance, the methods described in *J. Am. Chem. Soc.,* 74, 842 (1952), *Chem. Ber.,* 95, 937 (1962), or *J. Org. Chem.,* 29, 2887 (1964), or methods based on these methods. Furthermore, Compound (1a) is commercially available, or can be prepared by well-known methods other than those mentioned above.

Step II The reaction between Compound (1b) and Compound (1c) in this step is carried out at normal pressure or under pressure, without a solvent or in a suitable solvent.Specific examples of solvents include aromatic hydrocarbons, such as toluene and xylene; ketones, such as methylethylketone and methylisobutylketone; ethers, such as ether, tetrahydrofuran (THF), dioxane, and diglyme; alcohols, such as methanol (MeOH), ethanol (EtOH), and 2-propanol; acetonitrile, dimethylformamide (DMF), 1,3-dimethyl-2-imidazolidinone (DMI), dimethylsulfoxide (DMSO), water, or a solvent that is a mixture of these. It is preferred that this reaction be carried out in the presence of a base. Specific examples of bases include alkaline carbonates, such as sodium carbonate and potassium carbonate, alkaline hydrogen carbonates, such as sodium bicarbonate and potassium hydrogen carbonate, tertiary amines, such as triethylamine and diisopropylethylamine, and the like, and may be combined with an excess amount of Compound (1c).The reaction temperature differs according to the type of the raw material compound, the reaction conditions, and the like, and is generally between approximately 20°C and approximately 180°C, preferably between approximately 60°C and approximately 130°C.

[0015]

Preparation 2

[Formula 5]



(In the formula, Z' indicates the leaving group.)

This preparation is a method in which the boronic acid derivative, represented by Formula (2c), acts on a pyrimidine derivative, which has a leaving group, shown by Formula (2b), and which can be prepared by reacting the dihydroxypropylamine indicated by Formula (1c) with the pyrimidine derivate, which has two leaving groups, indicated by Formula (2a), to manufacture the compound shown by Formula (I).

The leaving group indicated by Z' in the Compounds (2a) and (2b) is the same as the leaving group indicated by Z in the Compound (1b) shown in Preparation 1, and Z and Z' may be the same or different.

Step I This step is performed based on the Step 2 in Preparation 1.

Note that, depending on the reaction conditions in Step 2, a compound can be used wherein the compound of (1c) is protected by a suitable protection group, the protection group being removed following Step 2.

Step II The condensation reaction in this step is carried out at normal pressure or under pressure, without a solvent or in a suitable solvent.

Specific examples of solvents include aromatic hydrocarbons, ketones, ethers, alcohols, acetonitrile, DMF, DMSO, water, or a solvent that is a mixture thereof. It is preferred that the present reaction be carried out in the presence of a base and specific examples of bases include alkaline carbonates,

alkaline hydrogen carbonates, tertiary amines, and the like. The reaction temperature differs according to the type of the raw material compound, the reaction conditions, and the like, and is generally between approximately 20°C and approximately 180°C, preferably between approximately 60°C and approximately 130°C.

Furthermore, this reaction may advance smoothly as a result of adding transition metals or transition metal-phosphine complexes. Specific examples thereof include palladium-carrying carbon, dichloro[1,4-bis(diphenylphosphine)butane]palladium, tetrakis(triphenylphosphine)palladium, and the like; those described in specific examples in U.S. Patent Publication No. 5550236 can also be used.

[0016]

Furthermore, some compounds shown by Formula (I) can also be prepared from compounds obtained in the manner described above, by combining any processes conventionally used by those skilled in the art, such as well-known alkylation, acylation, oxidation, and reduction.

[0017]

The compound of the present invention manufactured in this way is isolated/purified, either in free form, or as a salt thereof using ordinary salt formation processes. Isolation/purification is carried out by applying ordinary chemical operations, such as extraction, concentration, evaporation, crystallization, filtration, recrystallization, precipitation, and various chromatographies.

Various isomers can be isolated by ordinary methods, using the differences in physicochemical properties between the isomers. For instance, racemic mixtures can be used to produce an optically pure isomer by common separation methods for racemic bodies, such as, for instance, a method in which a diastereomeric salt is produced with a generic optically active acid, such as tartaric acid, and resolved optically. In addition, diastereo mixtures can be separated, for instance, by fractionation crystallization or various chromatographies and the like. In addition, optically active compounds can be manufactured by using raw materials with suitable optical activity.

[0018]

[Effects of the Invention]

The compound of the present invention, as indicated by Formula (I), has an excellent effect of promoting insulin secretion and an effect of suppressing blood sugar rise. Consequently, based on these effects, the compound shown by Formula (I) is useful in the treatment and/or prophylaxis of type 1 diabetes, type 2 diabetes, insulin-resistance diseases, and/or obesity.

[0019]

The pharmacological effects of the compound of the present invention have been verified by the following test methods.

(1) Test for measuring the effect of promoting insulin secretion

In this test, the effect of promoting insulin secretion was examined for the test compound using MIN6

cells or MIN6B1 cells, which are mouse pancreatic β cell strains.

The test method is described below.

MIN6 cells or MIN6B1 cells were sown in a 24-well plate so as to obtain 2 x 10^5 cells/well (0.4 ml) (culture medium used was DMEM containing 25 mM glucose to which FCS was added to 10%). After two days, the culture medium was removed with an aspirator, washed once with 1 ml of KRB-HEPES (140 mM NaCl, 3.6 mM KCl, 0.51 mM NaH_2PO_4, 0.5 mM $MgSO_4$, 1.5 mM $CaCl_2$, 2 mM $NaHCO_3$, 0.1% BSA, and 10 mM HEPES (pH 7.4)) containing 2.8 mM glucose warmed to 37°C; 1 ml of the same buffer solution was introduced again and incubated for between 30 minutes and 60 minutes at 37°C. The buffer solution was removed with an aspirator; 0.5 ml of KRB-HEPES containing 16.8 mM glucose to which 10 μM each of test compound had been added was added to each well and incubated for 22 minutes at 37°C. The samples were fractionated, and 2.0 μl to 2.5 μl were diluted in 50 μl of PBS; insulin concentration was determined using the Phadeseph insulin RIA kit (manufactured by Pharmacia, Upjohn) or a rat insulin [^{125}I] assay system RPA549 (Amersham Biosciences). The test compound was dissolved in 100% DMSO and added at a final concentration of 0.1%. The activity was expressed as a relative ratio where DMSO is 100%. The results are shown in Table 1. Note that, in the description of the compounds in the table, "Ex" indicates the example number of the example compound described below (same hereinafter).

[0020]

[Table 1]

Compound	Insulin secretion promoting effect (%)
Ex 26	167
Ex 34	178
Glibenclamide	122

As described above, the compound of the present invention showed a strong effect of promoting insulin secretion.

[0021]

(2) Test by oral sugar loading with normal mouse

In this test, the activity of the test compound in terms of suppressing blood sugar rise after sugar loading was examined using a normal mouse. The test method is shown below. An ICR mouse (male, 6 weeks old), prebred for 1 week, was fasted for 18 to 20 hours and used as test animal.

The test compound was dissolved in water and administered orally at 3 mg/kg (10 mg for Nateglinide) 5 minutes prior to glucose load (30 minutes before for Nateglinide).

The rate of blood sugar decrease (%) versus the control group 30 minutes after glucose loading was

measured. The results are shown in Table 2.

[0022]

[Table 2]

Compound	Rate of blood sugar decrease (%)
Ex 25	39
Ex 35	36
Nateglinide	26

As described above, the compound of the present invention showed a strong blood sugar lowering effect in the oral sugar loading test in the normal mouse.

[0023]

The pharmaceutical agent of the present invention can be prepared by methods used conventionally, using one or more of the compounds indicated by Formula (I) and an agent carrier, an excipient, and other additive agents used in conventional formulation. Administration may be in any form, including oral administration of tablets, pills, capsules, granules, powders, subtle granules, solutions, and the like, parenteral administration, such as via injectables, such as intravenous injection and intramuscular injection, or suppository, nasotracheal, transmucosal, percutaneous, and the like.

Tablets, powders, granules, and the like can be used as solid compositions for oral administration of the present invention. In such solid compositions, one or more active substance is mixed with at least one inert diluent, such as lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium aluminate metasilicate, or the like. According to ordinary method, the composition may contain an additive agent in addition to the inert diluent, for instance, a lubricant, such as magnesium stearate, a disintegrant, such as fibrous calcium gluconate, a stabilization agent, such as lactose, a solubilizer, such as glutamic acid or aspartic acid, or a dissolution adjuvant. Tablets or pills may be coated as necessary with a sugar coating, such as sucrose, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate, or a film soluble in the stomach or intestine.

[0024]

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs, and the like, and includes commonly used inert diluents, such as, purified water and EtOH. Such compositions may contain, in addition to the inert diluent, adjuvants, such as a solubilizer, a dissolution adjuvant, a wetting agent, a suspensioning agent, as well as sweetening agents, flavoring agents, aroma agents, and preservatives.

Injectables for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Diluents for aqueous solutions and suspensions include, for instance,

distilled water and physiological saline for injectables. As diluents for non-aqueous solutions and suspensions, for instance, propyleneglycol, polyethyleneglycol, plant oils, such as olive oil, alcohols, such as EtOH, and Polysorbate 80 (product name) are available. Such compositions may further contain additive agents, such as an isotonization agent, preservatives, a wetting agent, an emulsifying agent, a dispersant, a stabilization agent, such as, for instance, lactose, a solubilizer, or a dissolution adjuvant. These are sterilized by, for instance, filtration in which this is passed through a bacteria retaining filter, mixing this with bactericide, or irradiation. These may also be used by producing them as sterile solid compositions and dissolving these in sterile water or sterile injectable solvent prior to use.

In case of conventional oral administration, a daily dose of 0.1 to 500 mg per adult is adequate, and this is administered once or separated into two to four doses. In case of intravenous administration, a daily dose of 0.01 to 100 mg per adult is adequate, and this is administered once or separated into two to four doses. The dose is determined optimally according to each case considering the symptoms, age, body weight, sex, and the like. Since the dose varies due to a variety of factors, an amount less than the administration range described above may be sufficient.

[0025]

[Examples]

The present invention will be described below by way of examples; however, the present invention is not limited in any way by these examples.

In addition, the raw material compounds used in the examples also contain novel substances, and description will be given by taking preparations for such raw material compounds from well-known compounds as reference examples.

[0026]

Reference Example 1

After stirring a mixture of 31.32 g of 4-bromo-2,5-difluorobenzoic acid, 100 ml of thionyl chloride and 0.5 ml of DMF for 2 hours at 80°C, 200 ml of toluene was added and the solvent was eliminated by reduced pressure distillation. 200 ml of chloroform was added to the residue and 200 ml of 28% ammonium water was instilled in ice and this was stirred for 1 hour at the same temperature. The reaction solution was extracted with chloroform and, after washing the organic layer with a saturated saline solution (brine), this was dried with anhydrous magnesium sulfate ($MgSO_4$). The solvent was evaporated *in vacuo* to produce 28.42 g of 4-bromo-2,5-difluorobenzamide as a light yellow solid. The compound of Reference Example 2 was produced in the same manner as Reference Example 1.

[0027]

Reference Example 3

A mixture of 28.37 g of 4-bromo-2,5-difluorobenzamide and 115 ml of phosphorus oxychloride was stirred for 1.5 hours at 80°C, whereafter 250 ml of toluene was added and the solvent was evaporated *in*

vacuo. 300 ml of ice water was added to the residue, and after extraction with ether, the organic layer was washed with saturated aqueous sodium bicarbonate and brine, followed by drying with $MgSO_4$. The solvent was evaporated *in vacuo* to produce 26.82 g of 4-bromo-2,5-difluorobenzonitrile as a yellow solid. The compound of Reference Example 4 was produced in the same manner as Reference Example 3.

[0028]

Reference Example 5

Hydrochloric acid gas was blown for 30 minutes at –65°C into a mixture of 18.20 g of 4-bromobenzonitrile, 300 ml of chloroform, and 100 ml of EtOH while stirring, which was subsequently stirred overnight at room temperature. After evaporating the solvent *in vacuo*, 48 g of ammonium carbonate and 400 ml of EtOH were added to the residue and stirred for 3 days at room temperature. After adding 300 ml of water to the reaction solution, EtOH was evaporated *in vacuo*, and the deposited solids were collected by filtration, rinsed, and 22.91 g of 4-bromobenzamidine hydrochloride was obtained as colorless solids. The compounds of Reference Examples 6 to 10 were obtained in the same way as in Reference Example 5.

[0029]

Reference Example 11

To a 120 ml solution of MeOH containing 6.03 g of 3,4,5-trifluorobenzamidine, produced by dechlorinating 3,4,5-trifluorobenzamidine chloride, 3.74 g of sodium methoxide and 4.72 ml of methyl 3-oxopentanoate were added, and this was stirred for 14 hours at 60°C. To the reaction solution, 160 ml of an aqueous solution of 1 M HCl was added, the deposited solids were collected by filtration, rinsed, and 8.86 g of 6-ethyl-2-(3,4,5-trifluorophenyl)-3-H-pyrimidine-4-one was obtained as colorless solids. The compounds of Reference Examples 12 to 20 were obtained in the same manner as in Reference Example 11.

[0030]

Reference Example 21

A mixture of 5.83 g of 6-ethyl-2-(3,4,5-trifluorophenyl)-3-H-pyrimidine-4-one and 35 ml of phosphorus oxychloride was stirred for 2.5 hours at 100°C. After evaporating the solvent *in vacuo*, 50 ml of water was added to the residue and extracted with EtOAc. The organic layer was dried with $MgSO_4$, whereafter the solvent was evaporated *in vacuo* to produce 5.84 g of 4-chloro-6-ethyl-2-(3,4,5-trifluorophenyl) pyrimidine as a light brown noncrystalline solid.

The compounds of Reference Examples 22 to 30 were obtained in the same manner as in Reference Example 21.

[0031]

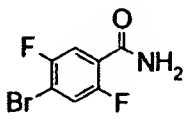
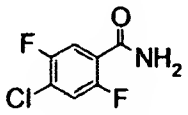
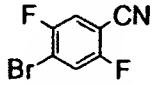
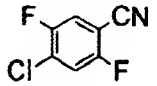
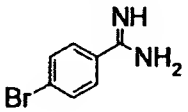
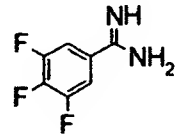
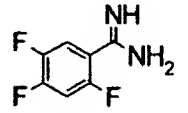
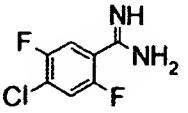
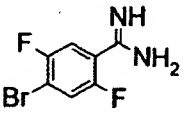
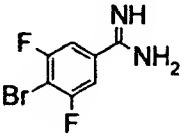
The structures and the physical data for the reference example compounds are shown in Tables 3 to

6. Note that the notations in the table have the following meanings (same hereinafter):

Rf: Reference Example number, Data: Physical data, FMS: mass spectrometric data (if not otherwise specified, FAB-MS(M+H)$^+$ data), NMR: NMR data ($(CH_3)_4Si$ serves as the internal reference, and if not otherwise specified, δ (ppm) of the peak in ^{1}H-NMR with DMSO-d_6 as the measurement solvent), Salt: Salt (HCl: hydrochloride, Ox: oxalate, unless otherwise specified: free-body), Structure: Chemical structure formula, Me: methyl, Et: ethyl.

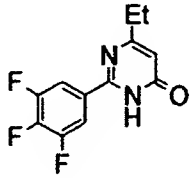
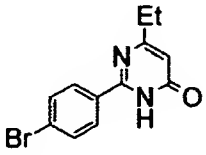
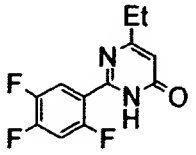
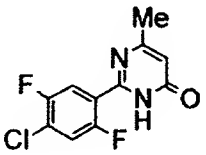
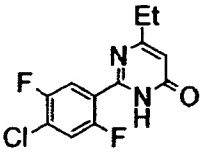
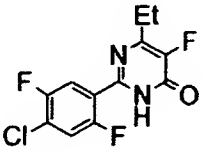
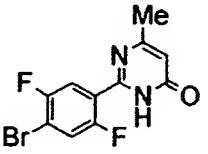
[0032]

[Table 3]

Rf (Salt)	Structure	Data
1		FMS:236,238.
2		FMS:192.
3		EI-MS(M^+):217,219.
4		EI-MS(M^+):173.
5 (HCl)		FMS:199,201.
6		FMS:175.
7		FMS:175.
8		FMS:191.
9		EI-MS(M^+):234,236.
10		FMS:237.

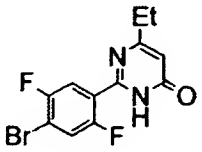
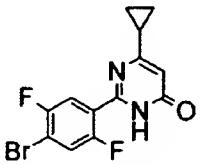
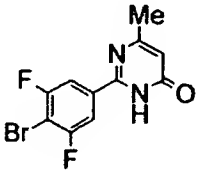
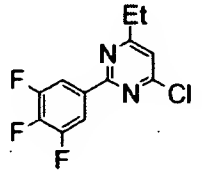
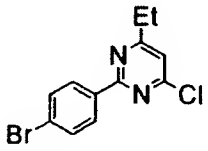
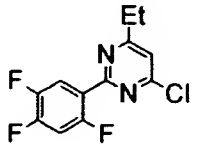
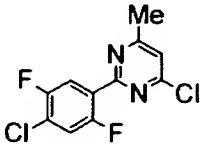
[0033]

[Table 4]

Rf (Salt)	Structure	Data
11		FMS:255.
12		FMS:279,281.
13		FMS:255.
14		FMS:257.
15		FMS:271.
16		FMS:289.
17		FMS:301,303.

[0034]

[Table 5]

Rf (Salt)	Structure	Data
18		FMS:315,317.
19		FMS:327,329.
20		FMS:301,303.
21		FMS:273.
22		FMS:299.
23		FMS:273.
24		FMS:275.

[0035]

[Table 6]

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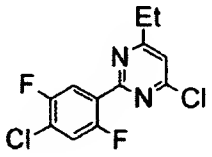
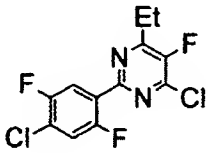
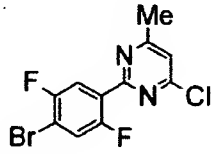
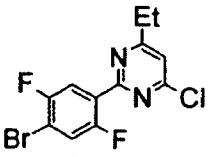
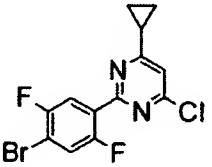
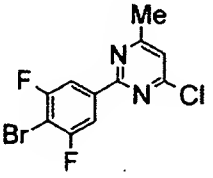
25		FMS:289.
26		FMS:307.
27		FMS:321.
28		FMS:333,335.
29		FMS:346.
30		FMS:319,321.

[0036]

Example 1

A mixture of 230 mg of 4-chloro-6-ethyl-2-(3,4,5-trifluorophenyl) pyrimidine, 650 ml of 3-amino-1,2-propanediol and 5 ml of acetonitrile was stirred for 15 hours at 80°C, whereafter 10 ml of water was added and this was extracted with ethyl acetate (EtOAc).The organic layer was washed with brine and dried with $MgSO_4$.The residue was purified by way of silica gel chromatography to produce 0.29 g of 3-{[6-ethyl-2-(3,4,5-trifluorophenyl) pyrimidine-4-yl]amino}propane-1,2-diol.

[0037]

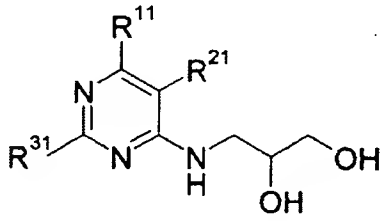
The structure and physical data for the example compounds described above are shown in Table 7. Furthermore, the structures and physical data for the example compounds obtained by the same methods as in Example 1, and the example compounds obtained by the same methods as in Example 1, using optically active 3-amino-1,2-propanediol, are shown in Tables 7 to 17. Note that the notations in the table have the following meanings (same hereinafter):

Ex: Example No.

R^{11}, R^{21}, R^{31}:Substituents in the general formulas (cPr: cyclopropyl, Ph: phenyl, Py: pyridyl, di: di, tri: tri. The numerals preceding the substituent denote the site of substitution. Accordingly, for example, 3-C1-4-F-Ph indicates 3-chloro-4-fluorophenyl and 6-Cl-3-Py indicates 6-chloropyridine-3-yl.)

[0038]

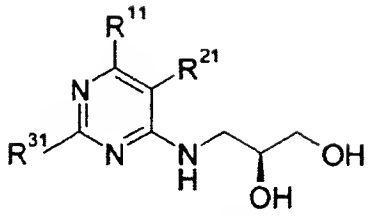
[Table 7]



Ex	R^{11} R^{21} R^{31}	Data
1	R^{11} : Et R^{21} : H R^{31} : 3,4,5-triF-Ph	NMR:1.29(3H,t),2.63-2.69(1H,br),2.64(2H,q), 3.41(1H,br),3.61-3.75(4H,m),3.94-3.96(1H,m) ,5.20(1H,br),6.18(1H,s),7.95-8.03(2H,m). FMS:327.
2 (Ox)	R^{11} : Et R^{21} : H R^{31} : 4-Br-Ph	NMR:1.22(3H,t),2.58(2H,q),3.00-3.50(3H,m), 3.50-3.80(2H,m),6.38(1H,s),7.00-7.60(1H,br), 7.67(2H,d),8.25(2H,d). FMS:352,354.

[0039]

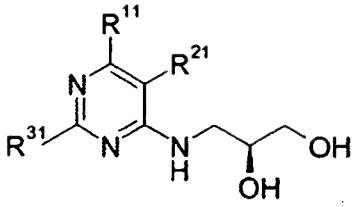
[Table 8]



Ex	R^{11} R^{21} R^{31}	Data
3 (Ox)	R^{11} : Et R^{21} : H R^{31} : 3-Cl-4-F-Ph	NMR:1.22(3H,t),2.58(2H,q),3.00-3.50(3H,m),3.50-3.80(2H,m),6.38(1H,s),7.20-7.80(2H,m),8.25-8.37(1H,m),8.43(1H,dd). FMS:326.
4 (Ox)	R^{11} : Et R^{21} : H R^{31} : 4-Cl-Ph	NMR:1.22(3H,t),2.58(2H,q),3.00-3.50(3H,m),3.50-3.80(2H,m),6.39(1H,s),7.20-7.90(3H,m),8.32(1H,d). FMS:308,Salt:$(CO_2H)_2$
5 (Ox)	R^{11} : Me R^{21} : H R^{31} : 2,5-diF-Ph	NMR:2.27(3H,s),2.90-3.60(4H,m),3.65(1H,quintet),6.40(1H,s),7.25-7.40(2H,m),7.40-7.60(1H,br),7.60-7.80(1H,m). FMS:296,Salt:$(CO_2H)_2$
6 (Ox)	R^{11} : Me R^{21} : H R^{31} : 4-Cl-2-F-Ph	NMR:2.28(3H,s),2.90-3.60(4H,m),3.65(1H,quintet),6.41(1H,s),7.39(1H,dd),7.51(1H,dd),7.55-7.80(1H,br),7.80-8.05(1H,m). FMS:312.
7 (Ox)	R^{11} : Et R^{21} : H R^{31} : 4-Br-3-F-Ph	NMR:1.21(3H,t),2.57(2H,q),3.00-3.50(3H,m),3.50-3.80(2H,m),6.39(1H,s),7.30-7.65(1H,br),7.81(1H,dd),8.11(1H,d),8.16(1H,d). FMS:370.
8 (Ox)	R^{11} : Me R^{21} : H R^{31} : 5-Br-2-F-Ph	NMR:2.28(3H,s),2.90-3.60(4H,m),3.65(1H,quintet),6.41(1H,s),7.29(1H,dd),7.40-7.75(2H,m),8.02(1H,d). FMS:356,358.
9 (Ox)	R^{11} : Me R^{21} : H R^{31} : 4-Cl-2,5-diF-Ph	NMR:2.27(3H,s),2.95-3.60(4H,m),3.64(1H,quintet),6.40(1H,s),7.20-7.60(1H,br),7.71(1H,dd),7.75-8.00(1H,m). FMS:330.

[0040]

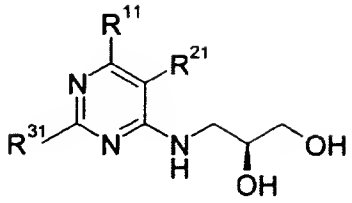
[Table 9]



Ex	R^{11} R^{21} R^{31}	Data
10 (Ox)	R^{11} : Me R^{21} : H R^{31} : 4-Br-3,5-diF-Ph	NMR:2.30(3H,s),2.95-3.50(3H,m),3.50-3.80(2H,m),6.40(1H,s),7.00-7.75(1H,br),8.03(2H,d). FMS:374,376.
11 (Ox)	R^{11} : Et R^{21} : H R^{31} : 4-Br-3,5-diF-Ph	NMR:1.22(3H,t),2.56(2H,q),3.00-3.50(3H,m),3.50-3.80(2H,m),6.41(1H,s),7.00-7.70(1H,br),8.05(2H,d). FMS:388,390.
12 (Ox)	R^{11} : Me R^{21} : H R^{31} : 6-Cl-3-Py	NMR:2.30(3H,s),2.95-3.50(3H,m),3.50-3.80(2H,m),6.40(1H,s),7.10-7.80(2H,m),8.61(1H,d),9.23(s,1H). FMS:295.
13 (Ox)	R^{11} : Et R^{21} : H R^{31} : 6-Cl-3-Py	NMR:1.22(3H,t),2.58(2H,q),3.00-3.50(3H,m),3.50-3.80(2H,m),6.41(1H,s),7.10-7.80(2H,m),8.62(1H,d),9.24(1H,s). FMS:309.
14 (Ox)	R^{11} : Et R^{21} : H R^{31} : 3,4-diCl-Ph	NMR:1.22(3H,t),2.58(2H,q),3.00-3.50(3H,m),3.50-3.80(2H,m),6.39(1H,s),7.00-7.65(1H,br),7.74(1H,d),8.28(1H,d),8.46(1H,s). FMS:342.
15 (Ox)	R^{11} : Et R^{21} : H R^{31} : 3,4,5-triF-Ph	NMR:1.21(3H,t),2.57(2H,q),3.00-3.50(3H,m),3.50-3.75(2H,m),6.39(1H,s),7.00-7.70(1H,br),8.11(2H,dd). FMS:328.
16 (Ox)	R^{11} : Me R^{21} : H R^{31} : 3,4,5-triF-Ph	NMR:2.28(3H,s),3.20-3.75(5H,m),6.37(1H,s),7.30-7.60(1H,br),8.00-8.02(2H,m). FMS:314.
17 (Ox)	R^{11} : Me R^{21} : F R^{31} : 3,4,5-triF-Ph	NMR:2.33(3H,d),3.25-3.50(3H,m),3.60-3.80(2H,m),7.54(1H,t),8.05(2H,m). FMS:332.

[0041]

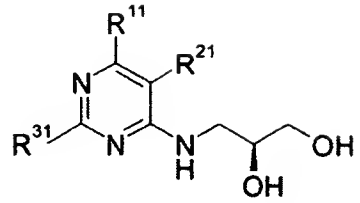
[Table 10]



Ex	R^{11} R^{21} R^{31}	Data
18 (Ox)	R^{11} : Me R^{21} : H R^{31} : 3-Cl-4-F-Ph	NMR:2.29(3H,s),3.20-3.50(3H,m),3.50-3.75(2H,m),6.37(1H,s),7.40-7.55(2H,m),8.30(1H,t),8.42(1H,m). FMS:312.
19 (Ox)	R^{11} : Me R^{21} : H R^{31} : 4-Cl-3-F-Ph	NMR:2.29(3H,s),3.25-3.50(3H,m),3.50-3.75(2H,m),6.38(1H,s),7.30-7.50(1H,br),7.68(1H,t),8.10-8.23(2H,m). FMS:312.
20 (Ox)	R^{11} : Me R^{21} : H R^{31} : 2,3,5-triF-Ph	NMR:2.28(3H,s),3.20-3.80(5H,m),6.41(1H,s),7.44-7.70(3H,m). FMS:314.
21 (Ox)	R^{11} : Et R^{21} : H R^{31} : 2,3,5-triF-Ph	NMR:1.20(3H,t),2.55(2H,q),3.20-3.70(5H,m),6.45(1H,s),7.40-7.70(3H,m). FMS:328.
22 (Ox)	R^{11} : Me R^{21} : H R^{31} : 2,4,5-triF-Ph	NMR:2.27(3H,s),3.10-3.70(5H,m),6.39(1H,s),7.35-7.70(2H,m), 7.80-8.05(1H,m). FMS:314.
23 (Ox)	R^{11} : Et R^{21} : H R^{31} : 2,4,5-triF-Ph	NMR:1.19(3H,t),2.54(2H,q),3.10-3.70(5H,m),6.39(1H,s),7.40-7.70(2H,m), 7.77-7.81(1H,m). FMS:328.
24 (Ox)	R^{11} : Me R^{21} : F R^{31} : 2,1,3-benzoxadiazol-5-yl	NMR:2.38(3H,d),3.38-3.50(3H,m),3.62-3.73(1H,m),3.74-3.84(1H,m),4.64(1H,t),4.87(1H,d),7.55-7.63(1H,m),8.11(1H,d),8.51(1H,d),8.79(1H,s). FMS:318.
25 (Ox)	R^{11} : Me R^{21} : H R^{31} : 4-Br-3-F-Ph	NMR:2.29(3H,s),3.20-3.75(5H,m),6.38(1H,s),7.30-7.55(1H,br),7.80(1H,t),8.00-8.25(2H,m). FMS:356.

[0042]

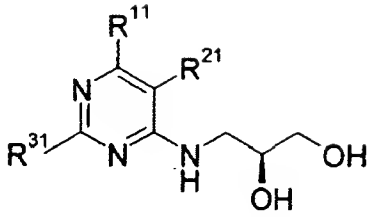
[Table 11]



Ex	R^{11} R^{21} R^{31}	Data
26 (Ox)	R^{11} : Me R^{21} : H R^{31} : 3,4-diCl-Ph	NMR:2.29(3H,s),3.20-3.75(5H,m),6.37(1H,s),7.73(1H,d),8.27(1H,d),8.45(1H,d). FMS:328.
27 (Ox)	R^{11} : Me R^{21} : H R^{31} : 4-Br-2-F-Ph	NMR:2.28(3H,s),3.10-3.75(5H,m),6.40(1H,s),7.40-7.70(3H,m),7.76-7.94(1H,m). FMS:356.
28 (Ox)	R^{11} : Me R^{21} : H R^{31} : 4-Cl-3,5-diF-Ph	NMR:2.29(3H,s),3.00-3.50(3H,m),3.50-3.80(2H,m),6.40(1H,s),7.00-7.75(1H,br),8.09(2H,d). FMS:330.
29 (Ox)	R^{11} : Et R^{21} : H R^{31} : 4-Cl-3,5-diF-Ph	NMR:1.22(3H,t),2.56(2H,q),3.00-3.50(3H,m),3.50-3.80(2H,m),6.40(1H,s),7.00-7.70(1H,br),8.10(2H,d). FMS:344.
30 (Ox)	R^{11} : Me R^{21} : H R^{31} : 2,1,3-benzoxadiazol-5-yl	NMR:2.34(3H,s),3.00-3.50(3H,m),3.50-3.80(2H,m),6.45(1H,s),7.00-7.75(1H,br),8.12(1H,d),8.55(1H,d),8.84(1H,s). FMS:302.
31 (Ox)	R^{11} : Et R^{21} : H R^{31} : 4-Cl-3-F-Ph	NMR:1.22(3H,t),2.57(2H,q),3.00-3.50(3H,m),3.50-3.80(2H,m),6.39(1H,s),7.00-7.60(1H,br),7.69(1H,dd),8.10-8.25(2H,m). FMS:326.
32 (Ox)	R^{11} : Et R^{21} : H R^{31} : 4-Cl-2,5-diF-Ph	NMR:1.19(3H,t),2.50-2.65(2H,m),3.10-3.70(5H,m),3.70-6.00(4H,m),6.45(1H,s),7.53(1H,brs),7.71(1H,dd),7.85-8.00(1H,m). FMS:344.

[0043]

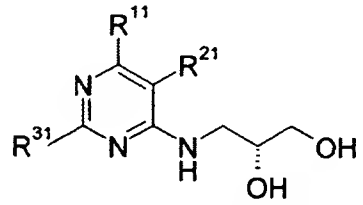
[Table 12]



Ex	R^{11} R^{21} R^{31}	Data
33 (Ox)	R^{11} : Et R^{21} : H R^{31} : 4-Br-2,5-diF-Ph	NMR:1.19(3H,t),2.55(2H,q),2.75-3.70(9H,m),6.42(1H,s),7.61(1H,br),7.77-7.93(2H,m). FMS:388,390.

[0044]

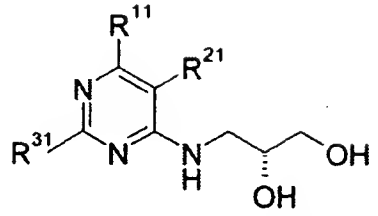
[Table 13]



Ex	R^{11} R^{21} R^{31}	Data
34 (Ox)	R^{11} : Et R^{21} : H R^{31} : 3,4,5-triF-Ph	NMR:1.21(3H,t),2.57(2H,q),3.00-3.50(3H,m),3.50-3.75(2H,m),6.39(1H,s),7.30-8.00(1H,br),8.11(2H,dd). FMS:328.
35 (Ox)	R^{11} : Et R^{21} : H R^{31} : 3-Cl-4-F-Ph	NMR:1.22(3H,t),2.58(2H,q),3.00-3.50(3H,m),3.50-3.80(2H,m),6.38(1H,s),7.20-7.80(2H,m),8.25-8.37(1H,m),8.43(1H,dd). FMS:326.

[0045]

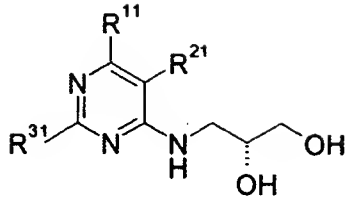
[Table 14]



Ex	R^{11} R^{21} R^{31}	Data
36 (Ox)	R^{11} : Et R^{21} : H R^{31} : 4-Cl-Ph	NMR:1.22(3H,t),2.58(2H,q),3.00-3.50(3H,m),3.50-3.80(2H,m),6.39(1H,s),7.20-7.90(3H,m),8.32(1H,d). FMS:308.
37 (Ox)	R^{11} : Et R^{21} : H R^{31} : 3,4-diCl-Ph	NMR:1.22(3H,t),2.58(2H,q),3.00-3.50(3H,m),3.50-3.80(2H,m),6.39(1H,s),7.00-7.65(1H,br),7.74(1H,d),8.28(1H,d),8.46(1H,s). FMS:342.
38 (Ox)	R^{11} : Et R^{21} : H R^{31} : 4-Br-3-F-Ph	NMR:1.21(3H,t),2.57(2H,q),3.00-3.50(3H,m),3.50-3.80(2H,m),6.39(1H,s),7.30-7.65(1H,br),7.81(1H,dd),8.11(1H,d),8.16(1H,d). FMS:370.
39 (Ox)	R^{11} : Me R^{21} : H R^{31} : 4-Cl-2,5-diF-Ph	NMR:2.27(3H,s),2.95-3.60(4H,m),3.64(1H,quintet),6.40(1H,s),7.20-7.60(1H,br),7.71(1H,dd),7.75-8.00(1H,m). FMS:330.
40 (Ox)	R^{11} : Me R^{21} : H R^{31} : 4-Cl-3,5-diF-Ph	NMR:2.29(3H,s),3.00-3.50(3H,m),3.50-3.80(2H,m),6.40(1H,s),7.00-7.75(1H,br),8.09(2H,d). FMS:330.
41 (Ox)	R^{11} : Et R^{21} : H R^{31} : 4-Cl-3,5-diF-Ph	NMR:1.22(3H,t),2.56(2H,q),3.00-3.50(3H,m),3.50-3.80(2H,m),6.40(1H,s),7.00-7.70(1H,br),8.10(2H,d). FMS:344.
42 (Ox)	R^{11} : Me R^{21} : H R^{31} : 4-Br-3,5-diF-Ph	NMR:2.30(3H,s),2.95-3.50(3H,m),3.50-3.80(2H,m),6.40(1H,s),7.00-7.75(1H,br),8.03(2H,d). FMS:374,376.

[0046]

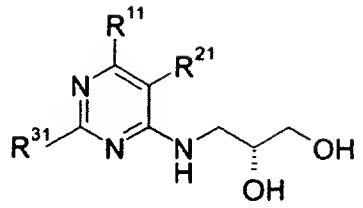
[Table 15]



Ex	R^{11} R^{21} R^{31}	Data
43 (Ox)	R^{11} : Et R^{21} : H R^{31} : 4-Br-3,5-diF-Ph	NMR:1.22(3H,t),2.56(2H,q),3.00-3.50(3H,m),3.50-3.80(2H,m),6.41(1H,s),7.00-7.70(1H,br),8.05(2H,d). FMS:388,390.
44 (Ox)	R^{11} : Et R^{21} : H R^{31} : 4-Cl-3-F-Ph	NMR:1.22(3H,t),2.57(2H,q),3.00-3.50(3H,m),3.50-3.80(2H,m),6.39(1H,s),7.00-7.60(1H,br),7.69(1H,dd),8.10-8.25(2H,m). FMS:326.
45	R^{11} : Me R^{21} : H R^{31} : 2,4,5-triF-Ph	NMR:2.26(3H,s),3.15-3.70(5H,m),4.50-4.65(1H,m),4.81(1H,d),6.36(1H,s),7.25-7.45(1H,m),7.55-7.65(1H,m),7.85-8.00(1H,m). FMS:314.
46 (Ox)	R^{11} : Et R^{21} : H R^{31} : 2,4,5-triF-Ph	NMR:1.19(3H,t),2.50-2.60(2H,m),3.10-3.70(5H,m),6.39(1H,s),7.40-7.60(1H,m),7.55-7.65(1H,m),7.85-8.05(1H,m). FMS:328.
47 (Ox)	R^{11} : Me R^{21} : H R^{31} : 2,1,3-benzoxadiazol-5-yl	NMR:2.33(3H,s),3.00-3.80(5H,m),4.50-5.00(2H,m),6.45(1H,s),7.45-7.60(1H,m),8.12(1H,d),8.56(1H,d),8.84(1H,s). FMS:302.
48 (Ox)	R^{11} : Me R^{21} : H R^{31} : 4-Cl-3-F-Ph	NMR:2.29(3H,s),3.15-3.75(5H,m),6.38(1H,s),7.40-7.60(1H,m),7.69(1H,t),8.10-8.25(2H,m). FMS:312.
49 (Ox)	R^{11} : Me R^{21} : H R^{31} : 4-Br-3-F-Ph	NMR:2.29(3H,s),3.10-3.70(5H,m),6.38(1H,s),7.30-7.60(1H,m),7.80(1H,t),8.09(1H,d),8.14(1H,d). FMS:356.

[0047]

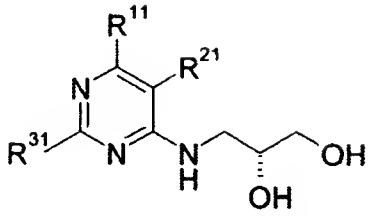
[Table 16]



Ex	R^{11} R^{21} R^{31}	Data
50 (Ox)	R^{11} : Me R^{21} : H R^{31} : 3,4-diCl-Ph	NMR:2.29(3H,s),3.20-3.70(5H,m),6.38(1H,s),7.35-7.55(1H,m),7.74(1H,d),8.26(1H,d),8.45(1H,d). FMS:328.
51 (Ox)	R^{11} : Et R^{21} : H R^{31} : 4-Cl-2,5-diF-Ph	NMR:1.19(3H,t),2.57(2H,q),3.00-3.45(3H,m),3.45-3.70(2H,m),6.41(1H,s),7.10-7.65(1H,br),7.71(1H,dd),7.80-8.05(1H,m). FMS:344.
52 (Ox)	R^{11} : Me R^{21} : H R^{31} : 4-Br-2,5-diF-Ph	NMR:2.27(3H,s),2.95-3.60(4H,m),3.64(1H,quintet),6.40(1H,s),7.10-7.65(1H,br),7.80(1H,dd),7.82-8.00(1H,m). FMS:374,376.
53 (Ox)	R^{11} : Et R^{21} : H R^{31} : 4-Br-2,5-diF-Ph	NMR:1.19(3H,t),2.55(2H,q),3.00-3.42(3H,m),3.42-3.70(2H,m),6.40(1H,s),7.10-7.65(1H,br),7.80(1H,dd),7.82-8.00(1H,m). FMS:388,390.
54 (Ox)	R^{11} : cPr R^{21} : H R^{31} : 4-Cl-2,5-diF-Ph	NMR:0.75-1.10(4H,m),1.75-2.05(1H,m),3.00-3.75(5H,m),6.44(1H,s),6.95-7.55(1H,br),7.68(1H,dd),7.80-8.00(1H,m). FMS:356.
55 (Ox)	R^{11} : cPr R^{21} : H R^{31} : 4-Br-2,5-diF-Ph	NMR:0.80-1.10(4H,m),1.75-2.05(1H,m),3.00-3.75(5H,m),6.44(1H,s),6.95-7.55(1H,br),7.77(1H,dd),7.80-8.00(1H,m). FMS:400,402.
56	R^{11} : Et R^{21} : F R^{31} : 4-Cl-2,5-diF-Ph	NMR:1.21(3H,t),2.67(2H,dq),3.25-3.42(3H,m),3.55(1H,dt),3.65-3.80(1H,m),4.57(1H,t),4.80(1H,d),7.50(1H,t),7.71(1H,dd),7.93(1H,dd). FMS:362

[0048]

[Table 17]



Ex	R^{11} R^{21} R^{31}	Data
57	R^{11} : Me R^{21} : F R^{31} : 4-Br-2,5-diF-Ph	NMR:2.32(3H,d),3.10-3.45(3H,m),3.55(1H,dt),3.65-3.80(1H,m),4.45-4.65(1H,m),4.80(1H,d),7.48(1H,t),7.79(1H,dd),7.86(1H,dd). FMS:392,394
58	R^{11} : CHF_2 R^{21} : H R^{31} : 4-Cl-2,5-diF-Ph	NMR:3.14-3.76(5H,m),4.62(1H,t),5.04(1H,d),6.78(1H,t),6.80(1H,s),7.50(1H,dd),7.92-8.80(2H,m). FMS:366.
59	R^{11} : Me R^{21} : Me R^{31} : 4-Cl-2,5-diF-Ph	NMR:2.03(3H,s),2.33(3H,s),3.30-3.40(3H,m),3.53-3.60(1H,m),3.68-3.76(1H,m),4.56(1H,t),4.79(1H,d),6.70(1H,t),7.68(1H,dd),7.92(1H,dd). FMS:344.
60 (Ox)	R^{11} : C_2F_5 R^{21} : H R^{31} : 4-Br-2,5-diF-Ph	NMR:3.25-3.75(4H,m),4.00-4.25(1H,m),7.04(1H,s),7.75-8.05(2H,m),8.20-8.50(1H,m). FMS:478,480.

[0049]

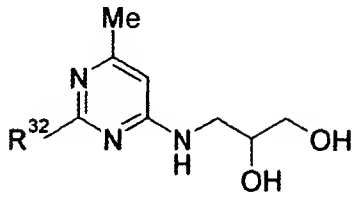
Below, the structures of other compounds of the present invention are shown in Table 18. These can easily be prepared using the methods described in the foregoing preparations and examples, methods that will be obvious to those skilled in the art, or variations on these methods. Note that, in the table, the notations have the following meanings.

No: Compound No.

R^{32}: Substituents in the general formulas (tBu: tertiary butyl).

[0050]

[Table 18]



No	R^{32}	No	R^{32}
A1	4-cyano-2,5-diF-Ph	A13	4-Me-Ph
A2	4-H_2N-2,5-diF-Ph	A14	4-$(Me_2N)O_2S$-Ph
A3	4-F_3C-Ph	A15	benzothiophen-5-yl
A4	4-Ph-Ph	A16	4-H_2NOC-2,5-diF-Ph
A5	1,3-benzodioxol-5-yl	A17	4-EtO_2C-2,5-diF-Ph
A6	4-HO-Ph	A18	4-H_2NOCHN-2,5-diF-Ph
A7	benzofuran-5-yl	A19	4-MeO-Ph
A8	1-Me-benzimidazol-5-yl	A20	4-O_2N-Ph
A9	4-HO_2C-2,5-diF-Ph	A21	4-tBu-Ph
A10	4-$(EtO_2C)HN$-2,5-diF-Ph	A22	indol-5-yl
A11	4-Me_2N-Ph	A23	5-Br-thiophen-2-yl
A12	4-F_3CO-Ph		